Clinical Section

Chemotherapy in Bacterial Infections

By

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The term chemotherapy literally means the treatment of disease by chemicals, but is now generally used in the narrower connotation defined by Ehrlich, as the treatment of parasitic diseases by chemicals with the object of destroying the specific parasite of the disease.

The oldest record of chemotherapy comes down from 1545 when followers of Pizaro in Peru brought back to Spain a bark which was used by the natives in the treatment of fevers and agues. Extracts and tinctures made from this bark were named chincona in honor of the Countess of Chinchon, who had become interested in the new remedy. The alkaloid quinine isolated much later from chincona bark, still remains a specific for malaria. At about the same period in Brazil the natives used ipecacuanha in the treatment of dysentry. However, the modern development of chemotherapy began with the brilliant researches of Paul Ehrlich at the beginning of this century.

In his studies of natural immunity Ehrlich realized that the defence of the body against certain infections, particularly those caused by protozoa, spirochaetes and trypanosomes, was inadequate to cure such infections and set up immunity. Obviously the problem of treatment of such parasitic diseases would have to be approached from some other angle.

He conceived the idea of producing substances by chemical synthesis which would have a special affinity for the protoplasm of the parasites with little toxic action on the host—in Ehrlich's own words—a substance maximally parasitotropic and minimally organotropic. This idea originated from his own side chain theory of immunity. He visualized the existance of side chains or chemo ceptors, which would endow the protoplasm with combining powers. Subsequent research has demonstrated that the action of chemotherapeutic agents is not as simple as this, but the theory inspired him to a laborious search for effective chemical agents.

He early became interested in the synthetic dyes, and noticed then curiously selective distribution in the various tissues of experimental animals. So he set to work, using thousands of white rats innoculated with a particular strain of trypanosomes, and injected them with many varieties of synthetic dyes. The walls of his laboratories were lined by cages of rats, whose noses, feet, tail and skin, exhibited every color in the rainbow — a riot of highly chromatic rodents, that sometimes sent visitors scuttling off to sign the pledge. From this exhaustive series of experiments has come some of the most important therapeutic agents used in treatment —to mention only a few—trypan red in trypanosomeoses, trypaflavine in sleeping sickness, salvarsan in syphilis.

The measure of success which has attended the chemotherapy of parasitic disease, has not been evident in the case of bacterial disease, although many agents have been tried. The substances which have been used as antiseptics for internal use may be classified as follows:

(1) Analine dyes { gentian violet, acroflavine, methylene blue }

(2) Ethylhydrocupriene and other cinchon derivatives.

(3) Compounds containing hypochlorites.

(4) Compounds of arsenic, mercury, mercurochrome, silver, gold.

(5) Phenols, Hexylresoicinol.

The history of these various substances has usually begun with a burst of enthusiasm, extravagant claims are made for the efficacy and non toxicity of a certain drug. This has been followed by a more critical appraisal of the drug with dwindling enthusiasm and a realization of many toxic effects which sharply limited its usefulness. Through these stages into the limbo have passed many chemotherapeutic agents since 1911. Many observers began to express grave doubts that any effective chemical agent would be found to combat bacterial disease.

However, early in 1935 Domagk in Germany reported a startling chemotherapeutic success. Haemolytic streptococci were injected into the peritoneum of 26 mice. One hour later 12 were given by stomach tube one dose of the dye now known as prontosil — all these mice survived, whereas 13 of the 14 controls were dead by the third day. Similar results were published shortly thereafter by Levaditi and Vaisman in France, who showed further that the subcutaneous injection of large amounts of prontosil in suspension frequently protected mice against a fatal dose of streptococcal culture injected 5 days later.

Early in 1936 Colebrooks and Kenny took up the study at Queen Charlotte Hospital. They showed that whereas a single dose of prontosil given by stomach tube or subcutaneous injection did not suffice to save mice infected one or two hours earlier by haemolytic streptococci, but subcutaneous injections repeated daily for 6 days were effective against 100—1,000 minimum lethal doses. The curative effects were obtained only against haemolytic streptococci of high mouse virulence. Their results in 38 cases of puerperal

fever due to haemolytic streptococci were most encouraging. At the same time Long and Bliss took up the investigation at Baltimore and confirmed the experimental and clinical results of Colebrook and Kenny. Since that time many reports attesting the efficacy of Prontosil and its derivatives in B—haemolytic streptococcal infections have appeared in this country and abroad. Additional evidence that these drugs are efficacious in infections by the meningococcus, and gonococcus, is now accumulating. There is also some evidence that Type III pneumococcal infections may be influenced by the exhibition of these drugs.

Chemical Constitution and Mode of Action.

Prontosil the original substance is an azo dye while the prontosil solution now used is a more complex compound—a 2.5 watery solution of disodium—4 sulphonamide phenyl 2—azo—7 acetyl—amino—1 hydroxynphaline.

Sulphanilimide is para-amino benzene sulphonamide.

It was noted by Colebrook and Kenny that solutions of Prontosil had no bacteriostatic effect on cultures of streptococci in vitro but that serum of patients who had received a dose of Prontosil had a definite bacteriostatic effect on cultures of streptococci. It was further shown that if prontosil were reduced by various agents such as magnesium powder, an active form capable of producing bacteriostasis was formed. Trefoull, Nitle and Bovet had reported previously that Sulphanilimide constituted the active fraction of prontosil, and this was quickly confirmed. It is therefore felt that the sulphanilimide radicle is the effective fraction of all these compounds, capable of producing bacteriostasis in cultures of susceptible organisms, and that in patients ill with streptococcal infections the prontosil solutions are reduced in the body to the active form of sulphanilimide.

The exact mode of action is yet undetermined. Domagk showed that prontosil therapy brought about a phagocytosis of haemolytic streptococci in infected mice, and thought that this was brought about by a destruction of the capsule. Long and Bliss later demonstrated that some time after injection of sulphanilimide into the peritoneal cavity of infected mice, a wave of phagocytosis occurred which proceeded until all the organisms were destroyed. They further showed that this was not effected by killing the organisms, but in some way of rendering them more susceptible to phagocytosis—somewhat akin to the action of opsonins.

The work of Marshall, Emerson and Cutting has shown that the drug sulphanilimide taken by mouth is completely absorbed within 3-5 hours and is largely excreted within 24 hours—partly in the unchanged state and partly in a conjugated form identified as para-acetyl-aminobenzene-sulphomide. They found that the drug passed rapidly into the spinal fluid and into empyema, ascitic and other body fluids. They demonstrated that renal impairment markedly retarded the excretion of the drug. Marshall has devised an accurate method of estimating the blood level of sulphanilimide thereby establishing control of a rational therapy.

Clinical Uses and Dosage.

Accumulated evidence shows that sulphanilimide and prontosil therapy is effective in most infections due to B—haemolytic streptococci. Non haemolytic strains are resistant to the action of these drugs. Sulphanilimide by mouth is the drug of choice, except in those cases where subcutaneous or parenteral administration seems desirable when Prontosil soluble—or a 1% solution of sulphanilimide in sterile saline is given.

Accurate dosage should be based on the criteria of Long and Bliss, which are derived from careful studies of the dose necessary to achieve a rapid elevation of blood level of 10 mgs. per cent. and to maintain such a level for varying lengths of time.

"In adult patients, that is those weighing 100 pounds or more, who are suffering from severe streptococcal infections, we administer an initial dose of from 10-16 five-grain tablets. This initial dose should give a blood level of 10 mgs. per cent within 4 hours. Then to maintain this level, we advise 3 five-grain tablets every 4 hours. If the patient weighs 50-90 pounds, the initial dose should be 6-10 five-grain tablets followed by 2 or 3 tablets at 4 hour intervals. In children weighing from 25-50 pounds, 4 to 6 five-grain tablets constitute the initial dose followed every 4 hours by 1 or 2 five-grain tablets. Patients excrete the drug at slightly different rates, so the maintenance dose may vary somewhat."

Prontosil solution should be given by the subcutaneous routes. It is absorbed rapidly and may be noted in the urine 15 minutes after injection. In adults the therapeutic dose of "prontosil solution" is 20 cc at 4 hour intervals, or a total of 120 cc of the solution in 24 hours. Individuals weighing 50-90 pounds should receive from 10-15 cc of the drug at four hourly intervals. Children 5-10 cc every 4 hours. These doses should be continued until a definite clinical improvement has been obtained, then gradually decreased. The doses recommended will color the skin pink and the urine bright red.

Prontosil solution is definitely irritating when given intrathecally and should not be administered by this route. Severe reactions may occur after intravenous injection.

Sulphanilimide solution (.8%—1% in physiological saline) may be given intrathecally in the treatment of meningitis, and is practically non-irritating. The solution is warmed to 37°C. and after spinal puncture has been completed an amount equivalent to 5-10 cc less than the amount of C.S. fluid which has been withdrawn is allowed to run into the spinal canal under the force of gravity. Intrathecal injections may be given every 8 hours.

The foregoing discussion concerns maximum

dosage used in severe streptococcal infections. In moderate infections 2 or 3 five-grain tablets of sulphanilimide every 4 hours may suffice.

In all cases after definite clinical improvement has been obtained the drug should be rapidly reduced. At the first sign of improvement the dose is cut by a third and if improvement is maintained the amount of the drug is reduced to one-third of the original amount. This final dosage is continued until convalescence is well under way.

Sulphanilimide may also be used as a prophylactic against streptococcal infections which occur in epidemics. In adults 2 five-grain tablets at 4 hour intervals usually suffice.

Pneumococcal Infections.

The status of sulphanilimide therapy in pneumococcal infections is as yet undetermined. Clinical experience with pneumococcal mastoiditis and middle ear infections tend to show some beneficial effect, but pneumonia has failed to respond in the majority of instances. Recently Heintzleman, Hodley and Mellon have reported the treatment of 9 cases of pneumonia due to a Type III pneumococcus with 7 recoveries. In a corresponding group of 10 patients observed during the same period but not receiving sulphonamide therapy, 2 recovered and 8 died. This work is suggestive but needs further corroboration.

Meningococcal Infections.

Buttle and Proom have demonstrated the protective and curative properties of sulphanilimide against meningococcal infections in mice, and a recent paper by Schwentker, Gilman and Long report the treatment of 10 cases of meningococcal meningitis and 1 case of meningococcal septicaemia by sulphanilimide alone. They obtained results comparable to the use of specific antiserum. Branham and Rosenthal compared the results of treatment of meningococcal infections in mice with sulphanilimide and with serum and combined therapy. These results showed that the combined drug and serum treatment was greatly superior to the use of either agent alone. We have recently employed this combined therapy in two cases of meningococcal meningitis in the Winnipeg General Hospital with very prompt and gratifying results.

Gas Gangrene.

A recent paper by Harold Bahlman suggests that the use of sulphanilimide may be of value in checking infection by B. Welchii when combined with conservative surgical measures. This work requires further confirmation.

Toxic Effects.

As with all new therapeutic agents, the initial wave of enthusiastic reports concurring the safety and efficacy of sulphanilimide and its derivatives in the treatment of infections, is now being followed by a rapid series of articles detailing the toxic effects of the drug. Thus the J.A.M.A. for September 25th contained no less than eight separate reports of toxic reactions to sulphanilimide.

So far Prontosil solution appears to have only one toxic effect and that is the *production of fever.* This is also seen in the use of sulphanilimide—a fact which must be kept in mind whenever the drug is employed.

Several mildly toxic effects of sulphanilimide therapy were described several months ago by many observers.

In normal persons a large dose of the drug frequently causes slight *dizziness* and *nausea.* These effects are sometimes seen in patients being treated with sulphanilimide who describe their sensations as being like a mild intoxication.

Cyanosis is noted in over three-quarters of the patients treated with sulpanilimide. This varies in intensity, and the exact mechanism of its production is unknown. Cyanosis is not an indication for withdrawal of the drug unless it is known to be caused be methaemoglobinaemia. A few patients have developed definite sulphaemoglobinaemia—usually due to the use of magnesium sulphate.

Practically all patients receiving sulphanilimide show a reduction in the CO^2 combining power of the blood, and occasionally a definite state of *acidosis* with air hunger may develop. In this reason it is wise to administer routinely 10 gr. of soda bicarbonate with each dose of sulphanilimide.

It must be born in mind that as all derivatives of sulphanilimide contain the *benzene ring*—injury to the haematopoietic system may occur in susceptible individuals. Thus 3 severe cases of haemolytic anaemia were recently reported by Janeway due to sulphanilimide and one additional case by S. E. Kohn during the past two weeks. Agranulocytosis has been recorded twice.

Cutaneous erruptions of various sorts appear to be among the commoner toxic reactions to sulphanilimide. A patient recently seen in the Winnipeg General Hospital developed an acute dermatitis following massive dosage of Prontylla. Several cases of photosensitivity with development of itchy maculopapular erruptions in those areas exposed to light have been reported in patients receiving sulphanilimide alone, and a number of instances of generalized dermatitis following its use appear in a recent journal. Schonberg has recently cited a case of allergic reactions to small doses of the drug, consisting of a purpuric erruption followed by a scarlatine form rash. Salvin also reports an instance of anyphylactic reaction and intense urticaria following administration of sulphanilimide for gonorrhoea in a patient with no previous history of hypersensitivity.

Paul Buay reports an instance of *toxic optic neuritis* following sulphanilimide therapy—on the first few administrations, headache, cyanosis, diarrhoea, and a choking sensation occurred, and finally the patient developed a severe loss of vision due to optic neuritis.

The accumulated experimental and chemical evidence of the past two years amply substantiates the initial claims that sulphanilimide and its derivatives are patent chemotherapeutic agents in the treatment of certain infections, but long continued clinical experience with these chemicals is necessary before they can be properly evaluated as therapeutic agents and the dangers attending their use clearly defined.

Proven Therapeutic Uses of Sulphanilimide.

1. B—Haemolytic Streptococci. (Not effective in non-haemolytic strains).
2. Meningococcal Infections.
3. Gonococcal Infections.
4. Pneumococcal Infections—especially Type 3. (combined Therapy).
5. B. Coli. and B. Proteus.
6. Gas Gangrene?
7. Undulant Fever?

Case Report

Bite from "Black Widow" Spider

by

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Souris, Man.

History: This patient, Mrs. M., age 41, was in usual health until the night of August 18th, when she was awakened suddenly from a sound sleep. She was trembling, and did not go back to sleep. She felt poorly in the morning and felt sharp stabbing pains in abdomen. She left for Winnipeg at 7 a.m. About 9 a.m. she noticed a picking sensation in left arm and a swelling about the size of a lemon. This swelling gradually increased and pain in the arm became severe towards evening. She commenced having severe chills about 11 a.m. and the abdominal pains increased in intensity. At 6 p.m. the temperature was 102, and later 103. She had general soreness and stiffness over the whole body. There was a sensation of something crawling on her neck at different times during the day and that night her daughter picked a large black spider off the arm and destroyed it.

Examination: I saw her first night of August 20th. She looked extremely ill. The temperature was 102, pulse 100 and weak. The posterior surface of the forearm was indurated and tender from wrist to elbow, and the hand was oedematous. Examination otherwise was negative.

Progress: Foments were applied to the arm and sedatives administered to relieve pain. The arm progressed to abscess formation and was opened on August 26th. The pus showed a short chain streptococci. Progress is now satisfactory.

Discussion: This patient was seen while in Winnipeg by Dr. Hartley Smith, who reported that there was a distinct mark on the arm which was characteristic of an insect bite. The history of finding a large black spider on the arm, the signs of an insect bite, and the course of the illness suggested the diagnosis is of a bite from a "Black Widow" spider.

Diagnosis: Bite from a "Black Widow" spider.

Special Articles and Association Notes

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Executive Meeting

Minutes of a special meeting of the Winnipeg members of the Manitoba Medical Association Executive held in the Medical Arts Club on Monday, November 29th, 1937, at 6.30 p.m.

Present.

Dr. C. W. Burns (Chairman)
Dr. C. W. MacCharles
Dr. W. W. Musgrove
Dr. E. W. Stewart
Dr. Digby Wheeler
Dr. W. G. Campbell
Dr. A. S. Kobrinsky
Dr. S. G. Herbert
Dr. E. S. Moorhead.

Guests.

Dr. T. C. Routley
Dr. F. W. Jackson.

The Chairman explained that the meeting had been called to discuss with Dr. Routley, the Secretary of the Canadian Medical Association, the question of the preparation of the brief by the Manitoba Medical Association which was to be forwarded to the Canadian Medical Association before the Canadian Medical Association prepared their brief for submission to the Rowell Royal Commission.

Dr. Routley explained that he had been instructed by the Executive Committee of the Canadian Medical Association to attend the meeting of the Royal Commission in each province and observe the proceedings, and note any points which might be brought up which would be of importance to the medical profession. He also explained that in the preparation of the brief which had to be submitted to the Royal Commission at Ottawa before January 1st, 1938, the Canadian Medical Association wished to have a brief from each Provincial Association from which to prepare the final document.

The question was discussed at length and various problems to be contained in the brief suggested. It was moved by Dr. W. W. Musgrove, seconded by Dr. A. S. Kobrinsky: That the Chairman appoint a committee to prepare a brief. —Carried.

Dr. Routley then explained the new scheme for Federation of the Canadian Medical Association and the various Provincial Medical Associations, and this was discussed in some detail.

Dr. Routley then stated that he wanted to know the name of a representative of the Manitoba Medical Association with which the Dominion Cancer Control Board could communicate. He also wanted to know if the Manitoba Cancer Relief and Research Institute would be agreeable to becoming the Manitoba Division of the Dominion organization for the control of cancer. The problem of cancer control was then discussed at length.

Dr. Routley wished an expression of opinion from the Manitoba Medical Association as to the proper method of disbursing monies from the King George V. Cancer Fund: Should the money be used for research, for education of the public, for education of the profession, or for active treatment of cases?

Dr. Routley advised that the question of holding a meeting of all the Secretaries of the various Provincial Medical Associations in Winnipeg at some suitable date, had been discussed.

The meeting then adjourned.

Minutes of a special meeting of the Executive of the Manitoba Medical Association held in the Medical Arts Club on Monday, December 6th, 1937, at 6.30 p.m.

Present.

Dr. C. W. Burns (Chairman)
Dr. C. W. MacCharles
Dr. Digby Wheeler
Dr. S. G. Herbert
Dr. H. O. McDiarmid
Dr. O. C. Trainor
Dr. E. W. Stewart
Dr. R. F. Yule
Dr. E. S. Moorhead
Dr. W. W. Musgrove
Dr. W. S. Peters
Dr. W. H. Clark.

Guest.

Dr. F. W. Jackson.

Re. Rowell Royal Commission.

The Chairman explained that the meeting had been called to consider the brief of the Manitoba Medical Association with regard to the Rowell

Royal Commission. The draft of the brief had been prepared by the committee appointed at the previous meeting. Mimeographed copies of the brief were handed to each member present at the meeting and time was allowed to study the copy.

The brief was discussed clause by clause and certain changes made in it.

A letter was then read by the Secretary from Dr. Gordon Chown, describing some of the difficulties of pediatrics in private practice resulting from the extending of free government services, particularly dealing with toxoid and numerating some objections to the activities of the public health nurses and social services generally interfering with medical practice. After various suggestions were considered section three of the brief was amended in order to include some of the principles enunciated in Dr. Chown's letter.

A preamble to the draft was then read.

It was moved by Dr. S. G. Herbert, seconded by Dr. E. W. Stewart: That the preamble be adopted. —Carried.

It was suggested by Dr. Peters that it should be pointed out to the Secretary of the Canadian Medical Association that there is no real public demand for health insurance in Canada. It was suggested that this should be pointed out in a covering letter with a copy of the draft and also that the Manitoba Medical Association would desire that the Canadian Medical Association should adhere to the eighteen points included in the report of the Committee on Economics at the Annual Meeting in Ottawa, June, 1937.

Dr. Musgrove brought up the question of patients who were able to pay who were admitted to public wards of large hospitals, but it was suggested that this was a matter to be dealt with by the local medical organizations and the hospitals concerned.

The Secretary was instructed to prepare a brief in the form indicated and forward to the Secretary of the Canadian Medical Association with a covering letter setting out the points enunciated by Dr. Peters and the reservations with regard to the discussion of health insurance. He was, also, instructed to write a letter to Dr. Chown indicating that the points in his memorandum had been considered and an attempt had been made to include them in the draft of the brief.

Cancer and King George V. Silver Jubilee Cancer Fund.

The President explained that the Secretary of the Canadian Medical Association had wanted to know the representative of the Manitoba Medical Association to whom the national organization dealing with cancer could communicate. It was suggested that Dr. Fahrni was one of the representatives of the Manitoba Medical Association on the Cancer Relief and Research Institute, and that he should fill this office. It was then pointed out that according to resolution passed at the Annual Meeting that the Cancer Relief and Research Institute should be the body to represent Manitoba Medical Association in any dealings with any National Organization concerned with cancer control.

It was moved by Dr. Digby Wheeler, seconded by Dr. S. G. Herbert: That a copy of this resolution should be sent to Dr. Routley. —Carried.

The question of the expenditure of monies available from the King George V. Silver Jubilee Cancer Fund, was then discussed. It was pointed out that the money in this fund had been subscribed by the public for the purpose of combatting cancer.

It was moved by Dr. Digby Wheeler, seconded by Dr. W. S. Peters: That the Secretary be instructed to write to the General Secretary of the Canadian Medical Association asking for information with regard to the amount of the King George V. Silver Jubilee Cancer Fund, the amount of interest available each year, the proposed method of spending the money, what body had been formed to spend the money, how much had been expended so far and to whom it had been given, and by whom such expenditure had been authorized. —Carried Unanimously.

Office of the Association.

Dr. Wheeler explained that he was negotiating with the Medical Arts Building to take over the space now occupied by the Manitoba Medical Association. A motion was put that the Executive approve of moving the office providing an arrangement satisfactory to all parties could be made. The motion was withdrawn.

It was then moved by Dr. O. C. Trainor, seconded by Dr. W. S. Peters: That a Committee consisting of the President, the Secretary, the Chairman of the Committee on Sociology, and the President of the Winnipeg Medical Society, to be appointed to deal with this question. —Carried.

The meeting then adjourned.

Manitoba Medical Association Brief for Canadian Medical Association for Submission to Rowell Royal Commission

PREAMBLE

The function of the profession of medicine is the alleviation, or cure of illness, the prevention of disease, the relief of human suffering, the prolongation of human life, and the promotion of the mental and bodily health of citizens by whatever means will attain these ends. The basic factor in the practice of medicine is the work of the practitioner dealing with an individual. There are, however, aspects of medical work which can be best carried out by groups of medical practitioners with scientific and technical assistants in

institutions such as hospitals and other organizations. There are also some parts of medical work which can be efficiently done only with the assistance of a government department.

There is no real line of demarcation between curative and preventative medicine, and it is the opinion of the Manitoba Medical Association that all medical work should be co-ordinated as much as possible to prevent duplication and waste of effort.

The Manitoba Medical Association submit that the following principles should be accepted by Government.

1. Canada should have a Dominion Department of Health, with a Minister in the Cabinet and a full time Deputy Minister whose time is devoted entirely and exclusively to health.

Many problems with regard to health which are common throughout the Dominion could be most efficiently dealt with by a department of the Dominion Government. Such a department could co-ordinate the efforts of the various Provinces and be prepared to furnish or secure scientific and technical assistance for the Provincial Health Departments, where such could not be provided by a single Province. Such problems are various aspects of industrial hygiene for example silicosis, also venereal disease, tuberculosis, cancer and special epidemics, such as acute anterior poliomyelitis, rocky mountain spotted fever, etc.

The Dominion Department of Health should be endowed with supervisary powers so that each Provincial Department of Health should attain to a certain minimum standard of efficiency.

2. All medical and health activities of the Dominion Government should be brought under the Department of Health, as has been already done in the case of the medical supervision of civil servants. Examples of these are the medical care of Indians, and the medical supervision of men employed on public works.

3. There are many preventive measures in medicine which are not now adequately used and increased efficiency would be aided by governmental action. Examples of such services are the giving of toxoid, vaccination, etc. The further employment of such preventive measures would not be an extravagance but would inevitably save money now spent on health and social services by individuals and governments. The public should be encouraged to make use of the preventive measures which can be given to them by private practitioners. Encouragement should be given to private physicians to carry out these measures. Free public health services of this type should be confined to the poor and indigent. Where a medical man is asked to undertake such work for the State either as a permanent official, a part time servant, or as a temporary appointee, he should be adequately paid.

4. Should a Government, Dominion or Provincial (preferably Dominion) desire to explore the possibilities of health insurance for wage earners or low income groups, the Manitoba Medical Association stands ready to co-operate in such an enquiry provided there is adequate representation from the medical profession on any commissions appointed to explore this problem.

5. That in the case of all persons provided either in whole or in part by the State, with the other necessities of life such as food, fuel, shelter and clothing, provision should likewise be made for medical services on the same basis. Examples of such persons are inmates of gaols, mental cases, old age pensioners, those on mothers' allowance, citizens in receipt of governmental unemployment relief funds, including unemployed assistance to pensioners and social welfare groups.

6. That with regard to medical appointments to the permanent, temporary or part time civil service, such appointments should be divorced from political consideration or interference. The Manitoba Medical Association stands ready to arrange for an advisory board to give an opinion on the medical qualifications of applicants. Further, all such vacancies should be adequately advertised in recognized medical journals, hospitals and medical schools, well in advance of the closing date for application.

Department of Health and Public Welfare

NEWS ITEMS

INFLUENZA

The following extracts have been taken from an article by Ronald Hare, M.D., published in "The Canadian Public Health Journal" April, 1937, on the recent advances in the study of Influenza. It may be of seasonal interest to physicians in this province.

There is no satisfactory definition of influenza. During epidemic periods it is characterized by a probable incubation period of about 48 hours and an abrupt onset with fever, malaise, and depression. Pains in the head, back and limbs are common. The fever lasts only for 3 or 4 days but recovery is usually slow with a considerable degree of prostration during convalescence. Coryza, pharyngitis, tracheitis and bronchitis may accompany the fever. Pneumonia may occur as a complication. There is generally a leucopenia. Finally, there is almost always evidence of extreme contagiousness. During an epidemic, cases are easily recognized but during inter-epidemic periods cases with the majority of these symptoms are comparatively common. Sometimes cases of common cold with an associated fever mimic epidemic influenza very successfully. It is probable, however, that such infections are not truly influenzal; but the differential diagnosis is not readily made and there is here a very considerable field of clinical research awaiting study.

AETIOLOGY

Two agents have been incriminated as the cause of influenza: a bacterium, H. influenzae, and more recently a virus.

H. Influenzae.

Since 1918, doubt as to the importance of H. influenzae has increased rather than diminished. Although this micro-organism can cause infections in man such as influenzal meningitis, its experimental instillation into the respiratory tract of animals has usually produced either no effect or symptoms that were not strongly suggestive of influenza as it occurs in human beings (McIntosh, 10). Similar instillation of cultures into human beings had not been extensively attempted until recently when Smorodinsteff et al (16) showed that a virulent strain of H. influenzae in inhilation experiments in human volunteers caused slight symptoms of infection of the respiratory tract but that several of the more typical symptoms of influenza were not produced, the illness was not contagious and a leucocytosis rather than a leucopenia resulted.

The importance of H. influenzae has rested almost solely on inference; it was said to be present in cases with the disease and absent or at least unusual in normal persons. That it is not invariably present in the disease has already been pointed out. The statement that it is only seldom present in normal persons will also have to undergo modification in view of the recent work of Fleming and MacLean (17) who showed that by employing a selective medium it is possible to demonstrate the presence of this micro-organism in from 90 to 100 per cent. of normal throats. Although the work of Pittman (18) has indicated it to be possible that a large proportion of such saprophytic strains were probably rough non-capsulated avirulent variants, the fact that H. influenzae was found so frequently in normal persons destroys one, at least, of the arguments brought forward in support of the hypothesis that it is the cause of epidemic influenza.

Virus.

Although prior to 1933 attempts had been made by various workers to show that a virus is the infective agent of influenza, these had been largely inconclusive for a variety of reasons. In that year, however, Smith, Andrewes and Laidlaw (19) showed that filtered nasopharyngeal washings from cases of epidemic influenza instilled into the nasal tract of ferrets would produce a febrile illness which could be transmitted to healthy ferrets in series by means of filtered suspensions of the tissue of the turbinate bones. A typical syndrome is produced which can be produced by no other material such as washings from normal throats or from cases of common colds. Indeed, washings from many cases of apparently typical epidemic influenza may fail to cause illness in the ferret.

Following inoculation, there is an incubation period of from 24 to 48 hours during which no change in the animal can be detected. The animal's temperature then rises to 104° F. or more but falls to normal (101-103° F.) during the next 24 hours. It then rises again and continues high for 2 to 4 days, finally becoming normal in from about 7 to 10 days. The temperature response is very variable in spacing and in degree but its diphasic character appears to be usual. During the period of the second rise in temperature, nasal symptoms such as a watery discharge which later becomes mucopurulent are common. At the same time the animal sneezes and yawns frequently, and there is excessive lachrymation. The animal is sluggish in movement and usually refuses food.

No virus inoculated direct from man has yet caused a sufficiently severe infection to kill the animal or even to cause pneumonia. But if passage-virus be employed and the instillation be carried out under ether, pneumonia occurs much more frequently and the resultant illness is more severe.

The disease in ferrets is highly contagious so that it can be transmitted to healthy ferrets merely by placing them in the same cage or even in the same room as an infected one. For this reason the experimental animals must be rigidly isolated from one another by a technique modelled on that employed by Laidlaw and Dunkin in their studies of canine distemper. The technique is extremely elaborate. Much space, time, and loyal co-operation by the staff of the animal room are required. Experimental studies were, however, facilitated by the indepedent discovery by Andrewes, Laidlaw and Smith (23) and by Francis (21) that the virus after passage through ferrets could infect mice if it were instilled into the nostrils under ether anaesthesia. Virus has never been transmitted direct to man from mice despite many attempts. Sometimes only one ferret-passage is required, more often several. The only pathological change seen in mice is a variable amount of red hepatisation of the lungs. There are no nasal symptoms. Probably for this reason the mouse infection is not contagious and, provided that ordinary cleanliness is practised, is not transmissible by contact.

The disease in mice is, on the whole, more severe than in ferrets. A large proportion of the mice die between the fourth and the seventh days. On post-mortem examination the most typical change is a variable amount of red hepatisation of the lungs, the substance of which is usually sterile when tested bacteriologically.

Washings from cases of human influenza instilled into the nostrils of swine will cause a mild afebrile illness (Elkeles, 22). Ferret or mouse virus will act in the same way (Shope and Francis, 24). But when virus is combined with a culture of H. influenzae suis (see below), a much more severe febrile illness closely resembling swine influenza is produced.

That the disease produced in ferrets and mice is due to the virus of human influenza is, of course, not yet completely proved. There is, however, no doubt

that a typical illness can be produced by the intranasal instillation of filtrates from influenza patients; that the infection of animals can be transmitted in series by bacteriologically sterile filtrates; and that the activity of such filtrates can be neutralized by the serum of convalescents from the disease. There is also evidence that human beings can become accidentally infected from animals in the acute stage of the animals' infection and that virus can be isolated from such accidental infections (Smith, Andrewes and Laidlaw, 19; Smith and Stuart-Harris, 25). Smorodinsteff et al (26) actually went further and showed that suspensions of virus instilled into the respiratory tract of five individuals brought about a typical attack of influenza.

Since the original observations in 1933, virus with similar properties and immunologically related to if not identical with the British strain has been isolated in outbreaks in various part of the world: Puerto Rico and Philadelphia (Francis, 21), Alaska (Francis, 21; Pettit, Mudd and Pepper, 27), New Haven, Conn. (Brightman, 28), Australia (Burnet, 29), Holland (Elkeles, 22) and Russia (Smorodinsteff et al, 26).

The Presence of Virus in the Disease.

During an epidemic period it would appear that it is relatively easy to isolate influenza virus provided, or course, that nasopharyngeal washings used are reasonably fresh and that the animals receiving instillations are fully susceptible. During sporadic outbreaks of disease closely resembling epidemic influenza, however, the presence of a virus frequently cannot be detected (Andrewes, Laidlaw and Smith, 30). The same applies to related illnesses such as febrile colds and la grippe. It may be that a virus is not responsible for such attacks, that a virus is present but that a susceptible animal has not yet been found, or that the influenza virus is responsible but too avirulent to cause infection in other animals. Needless to say, washings from normal throats or from convalescents are invariably without effect.

It was at first thought that all strains of human virus were serologically the same but Magill and Francis (31) have recently shown that differences may be detected between different strains.

THE PRESENCE OF ANTIBODIES IN THE SERUM OF NORMAL AND CONVALESCENT PERSONS

Neutralizing Antibodies.

It can be shown that persons recovering from epidemic influenza and animals recovering from the illness produced by human or swine influenza virus have neutralizing antibodies for the homologous virus in the serum (Smith, Andrewes and Laidlaw, 19; Shope, 35; Francis and Shope, 36). There is also evidence that the antibodies produced in response to infection with the human virus are distinct from antibodies produced after infection with the swine virus. On this basis it would appear that the human virus is serologically different from the swine virus (Smith, Andrewes and Laidlaw, 37; Francis and Shope, 36). On the other hand, if animals be hyperimmunized with the swine or the human virus their serum may acquire partial neutralizing power for the heterologous virus (with complete neutralizing power for the homologous virus), indicating that both viruses possess a common antigen (Francis and Shope, 40).

Specific neutralizing antibodies are found in the serum of a large proportion of normal human beings. A large number of investigations has been carried out in both England and the United States (Andrewes, Laidlaw and Smith, 30; Shope, 41; Francis and Magill, 38; Fairbrother and Hoyle, 39). Results obtained by these workers are given in Table I. It will be there seen that between 40 and 60 per cent. of adults possess antibodies for human virus but a much higher proportion, 60 to 100 per cent., for swine virus. In the younger age groups, and particularly amongst children

TABLE I

PERCENTAGE OF PERSONS OF VARIOUS AGES POSSESSING VIRUS-NEUTRALIZING ANTIBODIES FOR HUMAN AND SWINE VIRUS

Persons	Percentage of persons with neutralizing antibodies for Human Virus Per cent			Swine Virus Per cent		
Born after 1925	33	49	27	0	11	13
Born between 1916 and 1925	57	58	47	66	63	55
Born before 1916	62	48	46	100	92	63

Compiled from results obtained in England by Andrewes, Laidlaw and Smith (30), Fairbrother and Hoyle (39), and in America by Francis and Magill (38), and Shope (41).

in the first decade, antibodies for swine virus are unusual, only 0 to 13 per cent. possessing them, whereas a much higher proportion (27 to 50 per cent.) have antibodies for the human virus. These figures have led Laidlaw to make the interesting speculation in his Linacre lecture (42) that the 1918 pandemic of influenza was transmitted to swine in the autumn of that year and survives now as swine influenza, and that in human beings it died out, no virus of that type having to date been isolated from man. It was suggested further that the section of the population which went through the 1918 epidemic, and now comprising the age-group of 20 and over, acquired neutralizing antibodies for this virus in the process, whereas only a relatively small proportion of those who were born since 1918, and have therefore had no contact with this virus, have neutralizing antibodies. Human virus, on the other hand, being with us apparently year after year, seems to confer about the same amount of immunity on all age-groups.

Complement-fixing Antibodies.

Complement-fixing antibodies may be demonstrated in the serum of immunized animals, a proportion of normal individuals, and convalescent persons (Smith, 43; Fairbrother and Hoyle, 39).

ACTIVE IMMUNITY

Animals which have recovered from influenza are completely immune as soon as their temperature has reached normal and their symptoms have disappeared. This immunity is gradually lost so that in a few months a mild but definite illness follows instillation of virus. Thus there would appear to be little hope of obtaining an immunity to influenza for the rest of one's life, such as obtains in the case of several other virus diseases.

As already pointed out, influenza virus is infective only if it be instilled into the respiratory tract. If it is injected subcutaneously or intraperitoneally no infection occurs, but antibodies develop in the serum and the animals are subsequently found to be protected against pneumonia if not against infection. For this reason, attempts have been made to immunize groups of human beings by virus suspensions. Thus Francis and Magill (44) employed three subcutaneous or intradermal doses of the supernatant fluid of a tissue culture for immunization and showed that no symptoms and above all no infection resulted but that virus-neutralizing antibodies appeared in the serum and persisted for at least 5 or 6 months. No information is, of course, as yet available as to whether these individuals were protected against infection, nor do we yet know how long the antibodies persist.

Obviously the use of a living virus is open to many objections. Search has therefore been made for an immunizing vaccine in which the virus has been inactivated. Of the various types so far employed it would appear that one comprising formolized virus is most likely to be of value. Smith, Andrewes and Laidlaw (37) showed that such a vaccine would confer sufficient immunity on ferrets to protect them against lung lesions (employing a passage strain of virus which regularly produced pneumonia in controls). Andrewes and Smith (45) have recently shown that such a vaccine can confer complete immunity on mice. There

is thus a possibility that a safe and practicable method of protective inoculation for human beings may be developed eventually. There is, however, reason to believe that any immunity produced by these methods will be relatively short-lived and will probably require periodical reinforcement.

PASSIVE IMMUNITY

It is possible to obtain serum with virus-neutralizing antibodies by the injection of virus into horses and goats (Laidlaw, Smith, Andrewes and Dunkin, 46; Smith, 43). Such serum mixed with virus before instillation will completely prevent infection. If it be administered by injection after the virus has been instilled, the infection is modified and in many instances the life of the animals (mice) is saved. The earlier the serum is administered the more marked is the effect but nevertheless some effect can be noted even when the serum is administered as late as 72 hours after the virus.

A similar curative effect may be observed with serum from human convalescents; and several observers have reported good effects following the injection of human convalescent serum in influenzal pneumonia in human beings (McGuire and Redden, 47; McIntosh, 10; Kinsey, 48; and Hare, 49).

SUMMARY

For reasons which have already been given it would appear that H. influenzae is not the cause of epidemic influenza. This micro-organism may cause disease in the respiratory or cerebro-spinal tracts. It can cause infection and death of experimental animals, but there is no evidence that it alone is the cause of epidemic influenza. It may have importance on occasion as a secondary invader and may have had a synergistic action in the epidemic of 1918 as it appears to have now in swine influenza.

All the evidence at present points to a virus as the cause of epidemic influenza. This is rendered extremely probable by the facts that a filterable agent causes an infection in the ferret closely resembling human influenza, that material from such sick ferrets has caused an illness identical with epidemic influenza in human beings, that the serum of convalescents will neutralize the virus, and that the virus has not been demonstrated in normal throats.

That bacteria such as H. influenzae, haemolytic streptococci and pneumococci may take part in the disease process as complicating factors can hardly be doubted in view of the evidence acquired in 1918 and by consideration of present day swine influenza which is caused by the interaction of a virus (which itself closely resembles human influenza virus) and H. influenzae suis; but in neither human nor animal types of the disease is there any evidence that a bacterium is the primary causative agent.

There is circumstantial evidence that the 1918 epidemic of influenza in human beings was transmitted to the swine of the middle-western area of the U.S.A., where it has survived as swine influenza, closely related to and yet distinct from present-day epidemic human influenza. If this be the case, it opens up very interesting and important possibilities. If it is possible for human beings to transmit to an animal what is for it a new disease, it may prove to be equally possible for animals to transmit to humans a disease new to man. This may eventually prove to have been the actual origin of epidemics such as the influenza of 1918, for in view of the then world-wide incidence of this disease, it is wholly possible that we are dealing in that year with a virus new to man. It is therefore not outside the bounds of possibility that an animal virus which became adapted to human beings (and there is evidence that viruses may require adaptation before they will "take" in another animal species) was originally the cause of the pandemic. —C. R. D.

COMMUNICABLE DISEASES REPORTED

Urban and Rural - December, 1937.

Occurring in the Municipalities of:

Chickenpox: Total 377—Winnipeg 208, Brandon 85, The Pas 15, St. James 12, St. Boniface 5, Flin Flon 4, Tuxedo 2, Unorganized 2, Arthur 1, Dauphin Rural 1, Kildonan East 1, Kildonan North 1, La-Broquerie 1, Melita 1, St. Paul East 1 (Late Reported: November, Brandon 12, Shoal Lake Village 14, The Pas 5, Shoal Lake Rural 2, St. Boniface 2, Roblin Village 1, St. James 1).

Tuberculosis: Total 129—Portage City 27, Unorganized 21, Winnipeg 13, Cypress North 5, The Pas 5, Ethelbert 4, St. James 3, Bifrost 2, Cartier 2, Chatfield 2, Mossy River 2, Neepawa 2, Pembina 2, Rossburn Rural 2, Sifton 2, Stonewall 2, Winchester 2, Armstrong 1, Brandon 1, Clanwilliam 1, Daly 1, Dauphin Rural 1, Dauphin Town 1, Dufferin 1, Ellice 1, Ericksdale 1, Flin Flon 1, Franklin 1, Grandview Rural 1, Harrison 1, Kildonan East 1, Kildonan West 1, Lakeview 1, Miniota 1, Morton 1, Norfolk South 1, Portage Rural 1, Ritchot 1, Russell Rural 1, Saskatchewan 1, Shoal Lake Village 1, Siglunes 1, Swan River Town 1, St. Andrews 1, St. Boniface 1, St. Vital 1, Virden 1, Whitehead 1.

Scarlet Fever: Total 137—Winnipeg 58, Edward 12, Arthur 7, Morris Rural 6, Unorganized 6, Brandon 5, Springfield 5, St. Paul East 4, The Pas 4, Flin Flon 3, Portage City 3, Sifton 3, Ritchot 3, Bifrost 1, Brooklands 1, Kildonan North 1, Portage Rural 1, Rhineland 1, Souris 1, St. Boniface 1, Transcona 1 (Late Reported: October, Ritchot 1; November, Flin Flon 2, Morris Rural 2, Rockwood 2, Arthur 1, Melita 1, St. Francois 1.

Whooping Cough: Total 111—Winnipeg 20, Montcalm 13, St. Boniface 13, LaBroquerie 8, St. Vital 5, Transcona 4, Unorganized 3, Brandon 2, Flin Flon 2, Gimli Village 2, Blanshard 1, Hanover 1 (Late Reported: September, Coldwell 1, Odanah 1; October, Unorganized 1; November, Cornwallis 14, St. Boniface 8, Unorganized 5, Bifrost 1, Brooklands 1, Dauphin Town 1, Flin Flon 1, Fort Garry 1, Rockwood 1, Tache 1).

Measles: Total 65—Siglunes 19, Louise 7, Winnipeg 5, Portage City 2, Albert 1, Lorne 1, Oakland 1, St. Boniface 1 (Late Reported: October, Rossburn Rural 1; November, Rossburn Rural 25, Flin Flon 1. The Pas 1).

Mumps: Total 60—Winnipeg 24, Brandon 15, Unorganized 13, Transcona 2, Wallace 2, Arthur 1, Kildonan East 1, Minto 1, St. Boniface 1.

Influenza: Total 14—(Late Reported: August, Brokenhead 1; September, Silver Creek 1, Unorganized 2; October, Dufferin 1, Gimli Village 1, Unorganized 3, Glenella 1, Kildonan East 1, Odanah 1, Portage Rural 1, St. Clements 1).

Erysipelas: Total 10—Winnipeg 7, Boissevain 1, St. Anne 1, Unorganized 1.

Typhoid Fever: Total 10—Carman 3, Desalaberry 1, St. Boniface 1, Unorganized 1, Winkler 1 (Late Reported: July, Norfolk North 1; September, Tache 1; November, Unorganized 1).

Diphtheria: Total 7—Norfolk South 2, Winnipeg 2, Ritchot 1, Tache 1, Kildonan West 1.

Anterior Poliomyelitis: Total 5—(Late Reported: September, Transcona 5).

Cerebrospinal Meningitis: Total 2—Whitemouth 1 (Late Reported: November, Gimli Village 1).

German Measles: Total 2—Flin Flon 1, St. Boniface 1.

Diphtheria Carriers: Total 2—Winnipeg 2.

Puerperal Fever: Total 1—Whitemouth 1.

Typhoid Carriers: Total 1—Ste. Anne 1.

Venereal Diseases Reported: Total 138—Gonnorrhoea 92, Syphilis 46.

DEATHS FROM ALL CAUSES IN MANITOBA
For the Month of November, 1937.

URBAN—Cancer 37, Pneumonia 16, Tuberculosis 3, Whooping Cough 2, Syphilis 3, Meningoccal Meningitis 1, Puerperal Septicaemia 1, all others under 1 year 0, all other causes 151, Stillbirths 12. Total 226.

RURAL—Cancer 23, Pneumonia 16, Tuberculosis 13, Whooping Cough 4, Typhoid Fever 2, Infantile Paralysis 1, Influenza 1, Measles 1, Syphilis 1, all others under 1 year 4, all other causes 159, Stillbirths 3. Total 228.

INDIAN—Tuberculosis 24, Pneumonia 9, Influenza 2, all others under 1 year 5, all other causes 19, Stillbirths 2. Total 61.

MAP OF CANADA IN GREAT DEMAND

The Department of Mines and Resources has issued a third edition of the new map of Canada. This 100-mile-to-the-inch sheet has proved very popular and since it was first published about two years ago over 20,000 copies have been distributed to applicants in all parts of the Dominion and abroad. The new issue of 10,000 copies is to meet the continued demand for this map. The map shows the provinces, districts, railway lines, cities, towns, main rivers, and principal lakes and islands. It is 25 inches by 36 inches in size and is suitable for ready reference for general information about Canada's 3,694,863 square miles of territory.

Copies of the map may be obtained from the Surveyor General, Department of Mines and Resources, Ottawa, at 25 cents per copy. A copy will be furnished free to any school upon the application of the principal or school board.

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University of Manitoba

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RECENT STATEMENT BY THE JUDGES OF THE MEAD JOHNSON VITAMIN A AWARD

"The Vitamin A Award offered by Mead Johnso & Company was supposed to be made on the basis o papers published or accepted for publication by Dec ember 31, 1936. The judges of this award, meetin in New York, June 4, 1937, feel that its presentatio at this time is not warranted since no clinical inves tigation on vitamin A has yet been published whic completely answers any of the objectives of the origina proposal. The judges, therefore, agreed to defe further consideration of the granting of this awar until December 31, 1939. This action was take because of the existence of pronounced difference of opinion among investigators as to the reliabilit of any method yet proposed for determining the actua vitamin A requirements."

Statement by Mead Johnson & Company

In view of this action by the judges of the Mea Johnson Vitamin A Award, and as an earnest of ou good faith in the matter, we have segregated from ou corporate funds on deposit with the Continenta Illinois National Bank & Trust Company of Chicag the sum of $15,000. This cash deposit has been place in escrow and will be paid promptly when the boar of judges decides on the recipient of the Main o Clinical Award. The Laboratory Award of $5,00 was made on April 10th, 1935. —Adv